

01/09/90

BEST AVAILABLE COPY
CA Structure (1st & 2nd)

07/58,109

=> file registry
COST IN U.S. DOLLARS

redone
here

SINCE FILE
ENTRY
0.25

TOTAL
SESSION
0.25

FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 13:56:09 ON 09 JAN 91
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STRUCTURE FILE UPDATES: HIGHEST RN 131296-01-0
DICTIONARY FILE UPDATES: 06 JAN 91 (910106/ED) HIGHEST RN 131273-40-0

=> ~~act~~ adaman27a

L1 STR
~~(2)~~ (350)SEA CSS FUL L1

=> ~~file~~ ca

COST IN U.S. DOLLARS

SINCE FILE
ENTRY
0.56

TOTAL
SESSION
0.81

FULL ESTIMATED COST

FILE 'CA' ENTERED AT 13:56:52 ON 09 JAN 91
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FILE COVERS 1967 - 22 Dec 90 (901222/ED) VOL 113 ISS 26.
All OFFLINE Prints or Displays, use the ABS or ALL formats to obtain
abstract graphic structures. The AB format DOES NOT display structure
diagrams.

=> s 12

L3 ~~1470~~ L2

=> s ischemia or ischemic or ischaemia or ischaemic or hypoxia or hypoxic

- 11198 ISCHEMIA
- 3624 ISCHEMIC
- 24 ISCHAEMIA
- 31 ISCHAEMIC
- 8817 HYPOXIA
- 2173 HYPOXIC

_4 20083 ~~ISCHEMIA OR ISCHEMIC OR ISCHAEMIA OR ISCHAEMIC OR HYPOXIA~~
~~OR HYPOXIC~~

=> s anoxia or anoxic or stroke

- 1729 ANOXIA
- 1010 ANOXIC
- 934 STROKE

_5 3355 ~~ANOXIA OR ANOXIC OR STROKE~~

=> s 14 or 15

_6 22669 L4 OR L5

=> s alzheimer?

_7 1718 ALZHEIMER?

=> s 16 or 17

_8 24362 L6 OR L7

L9

4 L3 AND L8

=> d 19 1-6 bib ab

L9 ANSWER 1 OF 6

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AN CA113(21):184614j

TI Neuroprotective effect of memantine demonstrated in vivo and in vitro

AU Seif el Nasr, Mona; Peruche, Barbara; Rossberg, Christine; Mennel, Hans Dieter; Krieglstein, Josef

CS Inst. Pharmakol. Toxikol., Philipps-Univ.

LO Marburg D-3550, Fed. Rep. Ger.

SO Eur. J. Pharmacol., 185(1), 19-24

SC 1-11 (Pharmacology)

DT J

CO EJPHAZ

IS 0014-2999

PY 1990

LA Eng

AB The protective effects of the anticonvulsant memantine against hypoxic or ischemic damage were studied in a rat model of transient forebrain ischemia and cultured neurons from chick embryo cerebral hemispheres. Ischemia was induced for 10 min by clamping both arteries and lowering the mean arterial blood pressure to 40 mmHg; the rats were allowed to recover for 7 days. Cultured neurons were made hypoxic with 1 mM NaCN added to the incubation medium for 30 min followed by a recovery period of 3 days. The effects of memantine were compared with those produced by a typical non-competitive N-methyl-D-aspartate antagonist, dizocilpine. Similar effects were obtained with both drugs. The drugs reduced the damage caused by transient ischemia to neurons of the hippocampal CA1 subfield. Memantine (10 and 20 mg/kg) had a dose-dependent effect when administered i.p. to rats 1 h before ischemia. Dizocilpine was active at 1 mg/kg. When administered after ischemia, 10 mg memantine/kg protected CA1 neurons against ischemic damage. The 2 drugs protected cultured neurons against hypoxic damage. The lowest effective concn. was 0.1 μ M dizocilpine and 1 μ M memantine. Thus, memantine possesses neuroprotective activity but is less potent than dizocilpine.

L9 ANSWER 2 OF 6

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AN CA112(19):174876m

TI Amantadine and derivatives as modifiers of x-rays on mammalian cells

AU Alvarez, M. V.; Izquierdo, M. C.

CS Ist. Quim. Fis. "Rocasolano", CSIC

LO Madrid 28006, Spain

SO An. Quim., Ser. C, 85(1), 113-15

SC 8-6 (Radiation Biochemistry)

DT J

CO AQSRD6

IS 0211-1357

PY 1989

LA Spn

AB The x-ray modifying effects of amantadine (I) and 2 of its derivs. [1-adamantyl-4-nitropyrzole (II) and 1-(3-hydroxy-1-adamantyl)-4-nitropyrzole (III)] were studied in hamster tumor cell cultures under oxic and hypoxic conditions. I showed a moderate radiosensitizing effect under hypoxic conditions whereas II had no radiomodifying effect. III exhibited a radiosensitizing effect under hypoxic conditions even in the

AN CA112(15):138764q
TI Preparation of catechol derivatives for use in disorders of central nervous treatment
AU Fukazawa, Nobuyui; Otsuka, Kengo; Shimada, Shizuo; Miyama, Yukio; Ikeda, Fumiaki; Kaiho, Tatsuo
CS Mitsui Toatsu Chemicals, Inc.
LD Japan
SD ~~Suppl. J. Pharm. Med.~~, 22 pp
PR ~~EP 1989-032~~ ~~20 Sep 1989~~
DS R: CH, DE, FR, GB, IT, LI, NL, SE
AI EP 89-302742 20 Mar 1989
PRAI JP 88-63515 18 Mar 1988
JP 88-63516 18 Mar 1988
JP 88-201865 15 Aug 1988
JP 88-201866 15 Aug 1988
IC ICM C07C103-30
ICS A61K031-135; C07C103-26; C07D295-18; C07D207-16; C07D211-60; A61K031-16; A61K031-19; A61K031-215; A61K031-40; A61K031-445
SC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
SX 1
DT ~~45~~
CO EPXXDW
PY ~~1989~~
LA ~~Eng~~
AB Title compds. 1 [R1 = H, Ac; R2 = R3R4NCO, Q, R6R7N, CO2R8; R3, R4 = H, alkyl, cycloalkyl, (un)substituted aryl; R5 = H, alkyl (un)substituted aryl, alkoxy-carbonyl; X = bond, O, N, CH2; R6, R7 = H, alkyl, alkanoyl; R8 = H, alkyl; n = 1-3; (R1 = R6 = R7 = H and n = 2) and (R1 = R6 = H, R7 = Me, and n = 2) are excluded.], useful for treatment of progressive disorders of central nervous system including senile dementia of the Alzheimer type, are prepd. I also produce nerve growth factor (NGF) in particular tissues of the brain. Dihydrocaffeic acid in EtOH was refluxed in the presence of H2SO4 for 3 h to give 3,4-(HO)2C6H3CH2CH2CO2Et; to which in pyridine was added Ac2O to give I (R1 = Ac; R2 = CO2Et; n = 2). In test for promoting activity for prodn. and secretion of NGF in mouse cells, I (R1 = Ac; R2 = AcNH) at 0.2 mM showed a NGF increase ratio of 12.21.

AN CA109(23):207680m
TI The FMOC-ADAM approach to amino acid analysis
AU Betner, I.; Foeldi, P.
CS Pharmacia LKB Biotechnol. AB
LD Bromma S-16126, Swed.
SD ~~10-66, 66(9), 832, 834, 836, 838-40~~
SC 9-3 (Biochemical Methods)
OT ~~63~~
CO LCGCE7
IS 0888-9090
PY ~~1988~~
LA ~~Eng~~
AB Manual and automatic amino acid anal. by HPLC using automated precolumn derivatization with 9-fluorenylmethoxycarbonyl chloride (FMOC) and 1-aminoadamantane (ADAM) is described. Confirmatory expts. are presented, such as studies of reproducibility (CV values in the femtomole range). The limitations of the method are discussed, esp. with respect to the sensitivity, which is .apprx.50 fmol. Results are presented for analyses of protein hydrolyzate

L9 ANSWER 5 OF 6

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AN CA108(11):94948p

TI Preparation of vasopressin fragment derivatives as nootropics for treatment of senility

AU Goto, Giichi; Nagaoka, Akinobu; Wakimasu, Mitsuhiro

CS Takeda Chemical Industries, Ltd.

LO Japan

SO ~~Surv. Brain Res.~~ 68 pp.

PI ~~0037-0730/86/0002-0000\$02.00/0~~

DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE

AI EP 86-309800 16 Dec 1986

PRAT JP 85-291474 24 Dec 1985

IC ICM C07K007-06

ICS A61K037-02

SC 34-3 (Amino Acids, Peptides, and Proteins)

SX 2

DT P

CO EPXXDW

~~CA 1987~~

~~CA 1987~~

AB PGIu-Asp(NHR1)-Cys(H-Cys-OH)-A-D-Lys-B [I; R1 = H, C1-18 alkyl, (substituted) phenyl-C1-3 alkyl; A = amino, C1-6 alkylaminoacid residue; B = OH, amino, amino acid or amide] were prepd. as vasopressin fragment peptides, useful for treatment and prevention of dementia. PGIu-Asp-N-Cys(H-Cys-OH)-Pro-D-Lys-OH (II) was prepd. using soln.-phase methods, starting from BOC-D-Lys(Z)-OH.DCHA (BOC = tert-butyloxycarbonyl, Z = benzyloxycarbonyl, DCHA = dicyclohexylamine). II reversed cycloheximide-induced amnesia in mice when given intracerebroventricularly at 10 pg-10 ng.

L9 ANSWER 6 OF 6

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AN CA94(11):76956c

TI Dopaminergic agonists and conditioned avoidance response in normoxic or hypoxic rats

AU Saligaut, Christian; Moore, Nicholas; Leclerc, Jean Luc; Boismare, Francis

CS Dep. Pharmacol., Hotel-Dieu

LO Rouen 76031, Fr.

BO ~~Aviat. Space Environ. Med.~~ 57(1):15-23

SC 1-5 (Pharmacodynamics)

~~DI 1-5~~

CO ASEMCG

IS 0095-6562

PY 1981

LA Eng

AB The actions of 4 dopaminergic agonists, apomorphine [58-00-4], bromocriptine [25614-03-3], amantadine ~~[57-88-9]~~ [57-88-9], piribedil [3605-01-4] on a conditioned avoidance response were studied in normoxic or hypobaric hypoxic rats. Low doses of agonists have no effects in normoxia, but induce an antihypoxic-protection (improvement of learning in hypoxia). In contrast, the higher doses impair learning both in normoxia and hypobaric hypoxia. The possibility of an antihypoxic property induced by dopaminergic post-synaptic receptors stimulation is discussed and seems to be the main phenomenon whereas action on other nonspecific sites seems to be responsible for the high dose-induced impairment of learning and of resistance to hypoxia.

=> file registry

1991-10-11 10:00:00

1991-10-11 10:00:00

1991-10-11 10:00:00

FULL ESTIMATED COST

ENTRY
21.60

SESSION
22.41

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

DAY SUBSCRIBER PRICE

ENTRY

SESSION

-2.04

-2.04

FILE 'REGISTRY' ENTERED AT 14:02:32 ON 09 JAN 91

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STRUCTURE FILE UPDATES: HIGHEST RN 131296-01-0

DICTIONARY FILE UPDATES: 06 JAN 91 (910106/ED) HIGHEST RN 131273-40-0

=> structure

ENTER NAME OF STRUCTURE TO BE RECALLED (NONE):adaman1/q

ENTER (DIS), GRA, NOD, BON OR ?;dis

Structure (2nd)
(cyclic around NOD 13)

```

              13
            15
          G1 ----N----G1
              -      14
              -
              C
          1   - - - - 5
            C 4 - - 2 - - C
              -   C   -
              -   -   -
              -   -   -
          18 G2 ----C - - - - C ----G1 16
              - 3 - - - - C - - - 9
              -   -   -
              -   8 - - 7 - -
              -   C - - -
              -   -   -
          6 C- - - - - C
              17 G2: 10
C+++++C++++C++++C++++C

```

019 20 21 22 23

C+++++C++++C++++C++++C+++++C

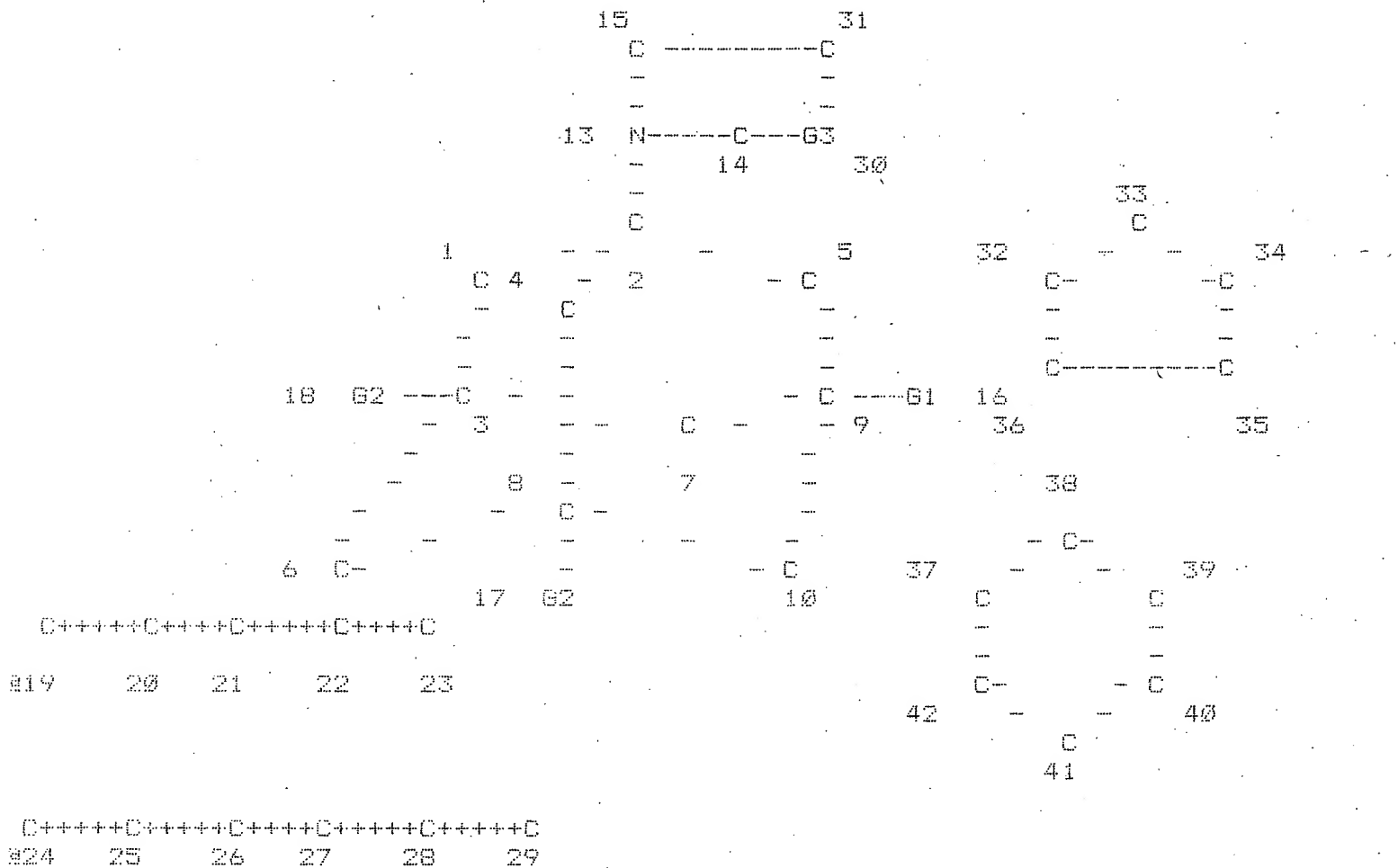
024 25 26 27 28 29

VAR G1=H/ME/ET/I-PR/N-PR/N-BU/I-BU/S-BU/T-BU/19/24

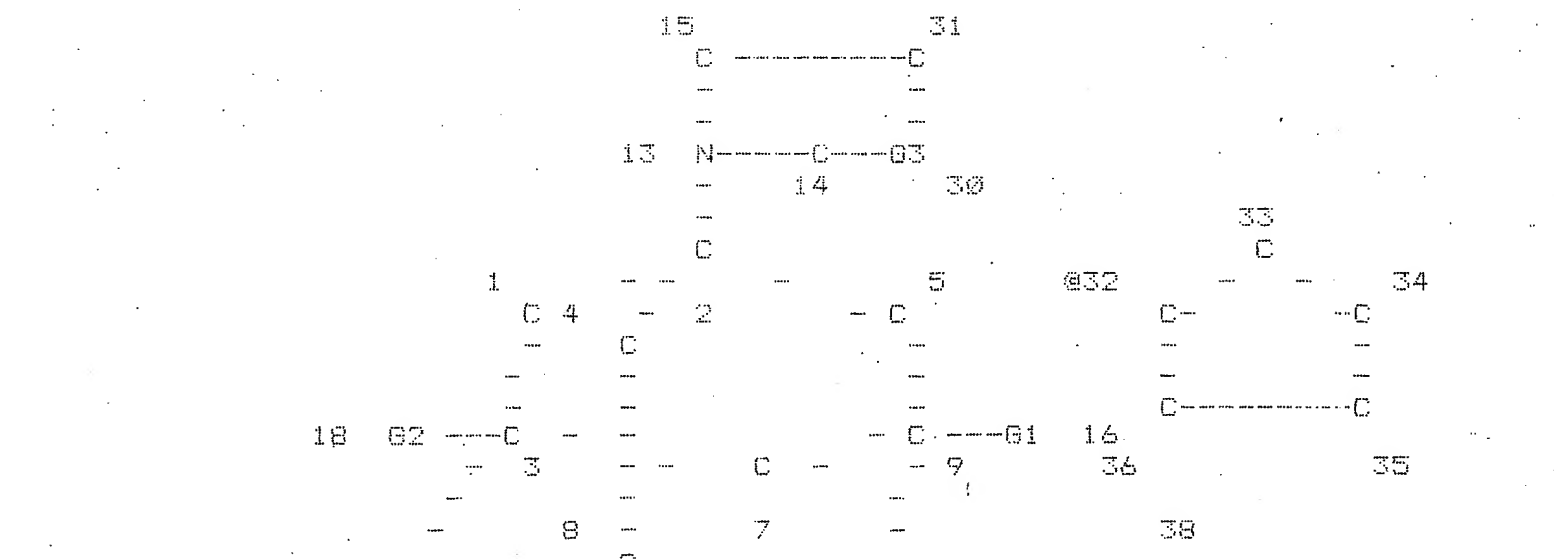
VAR G2=H/ME/ET/I-PR/N-PR/N-BU/I-BU/T-BU/S-BU/19/24/PH

ENTER (DIS), GRA, NOD, BON OR ?;

ENTER (DIS), GRA, NOD, BON OR ? :dis



VAR G1=H/ME/ET/I-PR/N-PR/N-BU/I-BU/S-BU/T-BU/19/24
VAR G2=H/ME/ET/I-PR/N-PR/N-BU/I-BU/T-BU/S-BU/19/24/PH
REP G3=(1-2) C
ENTER (DIS), GRA, NOD, BON OR ? :var g2=h/me/et/i-pr/n-pr/n-bu/t-bu/s-bu/19/24/ph
/32/37
32 IN USE. CHANGE?(Y)/N:y
ENTER (DIS), GRA, NOD, BON OR ? :dis



C++++C++++C++++C++++C++++C
@24 25 26 27 28 29

VAR G1=H/ME/ET/I-PR/N-PR/N-BU/I-BU/S-BU/T-BU/19/24
VAR G2=H/ME/ET/I-PR/N-PR/N-BU/T-BU/S-BU/19/24/PH/32/37

REP G3= (1-2) C

ENTER (DIS), GRA, NOD, BON OR ? : rep 32

ENTER (DIS), GRA, NOD, BON OR ?; resp 37, dis sat

NODE ATTRIBUTES: NONE

GRAPH ATTRIBUTES:

RSPEC 2 32 37

NUMBER OF NODES IS 40

ENTER (DIS), GRA, NOD, BON OR ? :end

...10 STRUCTURE CREATED

```
=> say 110 adaman3/q
```

$$\Rightarrow 5 \mid 110$$

SAMPLE SEARCH INITIATED 14:36:59

SCREENING

SAMPLE SCREEN SEARCH COMPLETED - 38 TO ITERATE

100.0% PROCESSED 38 ITERATIONS

3 ANSWERS

SEARCH TIME: 00.00.44

FULL FILE PROJECTIONS: ONLINE **COMPLETE**

BATCH **COMPLETE**

PROJECTED ITERATIONS: 391 TO 1129

PROJECTED ANSWERS: 3 TO 163

..11 3 SEA 555 6AM L10

=> s 110 cse ful

FULL SEARCH INITIATED 14:38:18

FULL SCREEN SEARCH COMPLETED - 583 TO ITERATE

100.0% PROCESSED 583 ITERATIONS

4 ANSWERS

SEARCH TIME: 00.00.27

_12 4 SEA CSS FUL L10

```
=> sav 112 adaman4/a
```

$$\Rightarrow d \mid 112 \quad 1-4$$

..12 ANSWER 1 OF 4

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3N 22947-47-3

CN Piperidine, 1-(1-adamantyl)- (BCI) (CA INDEX NAME)

FB 3D CONCORD

YF C15 H25 N

..C BELLESTEIN, CA

... ..

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RN 19984-43-1

DN	Piperidine, 1-(1-adamantyl)-, hydrochloride (BCI)	(CA INDEX NAME)
----	---	-----------------

CC15H25N.C1H

...C CA, IFICDB, IFIFAT, IFIUDB

④ HCl

2 REFERENCES IN FILE CA (1967 TO DATE)

_12 ANSWER 3 OF 4

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RN 3728-71-0

CN Pyrrolidine, 1-(1-adamantyl)- (7CI, 8CI) (CA INDEX NAME).

79 3D CONCORD

MF . C14 H23 N

..C. BEILSTEIN, CADLD

REFERENCES IN FILE CAOLD (PRIOR TO 1967)

8 REFERENCES IN FILE CA (1967 TO DATE)

...12 ANSWER 4 OF 4

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NAME)
 MF C14 H23 N . C1 H
 LC CA, CAOLD, IFICDB, IFIPAT, IFIUD8

 ..C...C
 C. . .
 . C. . C .C
 C. NC....C .
 . . . C....C
 . C....C C

@ HCl

REFERENCES IN FILE CAOLD (PRIOR TO 1967)
 3 REFERENCES IN FILE CA (1967 TO DATE)

=> file ca

COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
127.28	149.69

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE ENTRY	TOTAL SESSION
0.00	-2.04

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 diagrams.

=> s 112

_113 5 L12

=> d 113 1-5 bib ab

_113 ANSWER 1 OF 5

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AN CA75(11):76237b

TI Antiviral agents. 2. Structure-activity relations of compounds related to 1-adamantanamine

AU Aldrich, Paul E.; Hermann, Edward C.; Meier, Walter E.; Paulshock,
 Marvin; Prichard, William W.; Synder, Jack Austin; Watts, John C.

CS Exp. Stn., E. I. du Pont de Nemours and Co.

LD Wilmington, Del., USA

30 J. Med. Chem., 14(6), 535-43

SC 24 (Alicyclic Compounds)

DT J

CO JMCNAR

NY 1971

LA Eng

AB A no. of compds. related to 1-adamantanamine (I) was prepd. by

N-substituted carbamides and/or the carbamic acid esters. They were tested for the antiviral activity against influenza A virus. None of the N-substituted derivs. of I exhibited greater activity than I itself. Insertion of 1 or more C atoms between N and adamantane nucleus of I caused increased activity. The members of the tricyclo[4.3.1.1]undecane(homoadamantane) system were active. The resolved or racemic mixt. of rimantadine-HCl (II) and .alpha.,.alpha.-dimethyltricyclo[4.3.1.1]undecane-3-methylamine-HCl (III) were the most potent ~~antiviral~~ agents among 87 compds. tested.

LI3 ANSWER 2 OF 5

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AN CA71(3):12643r
 TI Adamantane and its derivatives. XVIII. Reaction of 1-bromoadamantane with amines
 AU Stepanov, F. N.; Stolyarov, Z. E.
 CS Kiev. Politekh. Inst.
 LO Kiev, USSR
 SO Zh. Org. Khim., 5(3), 537-41
 SC 24 (Alicyclic Compounds)
 DT J
 CO ZORKAE
 PY 1969
 LA Russ
 AB Aliphatic primary amines react with 1-bromoadamantane (I) only at 170-80.degree. (sealed tube reaction). Aliphatic secondary amines require 200-10.degree. to react with I. Also prepd. was 1,1'-diadamantylamine. The aromatic amines react with I in 2 ways. Thus PhNH2 gave .apprx.20% N-(adamant-1-yl)aniline (II) and .apprx.7% 4-(adamant-1-yl)aniline. Similarly, o-MeC6H4NH2 reacted with I to give 26.2% 2-methyl-4-(adamant-1-yl)aniline and 4.1% 2-methyl-N-(adamant-1-yl)aniline. However, m-MeC6H4NH2 or p-MeC6H4-NH2 gave only 3-methyl-N-(adamant-1-yl)aniline (III) or 4-methyl-N-(adamant-1-yl)aniline, resp. PhNMe2 also gave only 1 product: 4-(adamant-1-yl)dimethylaniline. The methylation of II or III gave, resp., N-methyl-N-(adamant-1-yl)-aniline and 3-methyl-N-methyl-N-(adamant-1-yl)aniline. The tertiary amines, due to the steric hindrance, are not conjugated through the central N atom.

LI3 ANSWER 3 OF 5

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AN CA69(21):86455m
 TI Adamantylamines by direct amination of 1-bromoadamantane
 AU Krumkalns, Eriks V.; Pfeifer, William
 CS Eli Lilly and Co.
 LO Greenfield, Indiana, USA
 SO J. Med. Chem., 11(5), 1103
 SC 24 (Alicyclic Compounds)
 DT J
 CO JMCMAR
 PY 1968
 LA Eng
 AB Unavailable

LI3 ANSWER 4 OF 5

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AN CA69(15):59201v
 TI Adamantyl secondary amines
 AU Mills, Jack; Krumkalns, Eriks
 CS Lilly, Eli, and Co.
 SO U.S., 4 pp.
 PY 1968

NCL 260268000
SC 26 (Heterocyclic Compounds (More Than One Hetero Atom))
DT P
CO USXXAM
PY 1968
LA Eng
AB Unavailable

L13 ANSWER 5 OF 5

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AN CA67(3):11275c
TI 1-Aminoadamantanes
AU Paulshock, Marvin; Watts, John C.
CS du Pont de Nemours, E. I., and Co.
SO U.S., 10 pp.
PI US 3310469 21 Mar 1967
AI US 22 Oct 1963 - 5 May 1966
NCL 167065000
SC 24 (Alicyclic Compounds)
DT P
CO USXXAM
PY 1967
LA Eng
AB Unavailable

=> = ~~FL3 and 14~~

-14

=>



01/08/91

APS

67/508,109

=> ischemia or ischemic or ischaemia or ischaemic or hypoxic or hypoxia or anoxia or anoxic or stroke or strokes

926 ISCHEMIA
1352 ISCHEMIC
198 ISCHAEMIA
315 ISCHAEMIC
333 HYPOXIC
523 HYPOXIA

08 JAN 91 09:14:24

U.S. Patent & Trademark Office

P0013

343 ANOXIA
256 ANOXIC
70782 STROKE
17351 STROKES

_7 77929 ISCHEMIA OR ISCHEMIC OR ISCHAEMIA OR ISCHAEMIC OR HYPOXIC OR HYPOXIA OR ANOXIA OR ANOXIC OR STROKE OR STROKES

=> s alzheimer or alzheimers or alzheimer's
MISMATCHED QUOTE 'ALZHEIMER'S'

=> s alzheimer?
_8 352 ALZHEIMER?

=> s 18 and 17
_9 92 L8 AND L7

08 JAN 91 09:16:00

U.S. Patent & Trademark Office

P0014

=> s adamantane? or ?adamantane or ?adamantanes

845 ADAMANTANE?
900 ?ADAMANTANE
122 ?ADAMANTANES

_10 1063 ADAMANTANE? OR ?ADAMANTANE OR ?ADAMANTANES

=> s 110 and 19
_11 1 L10 AND L9

=> d 111

1. 4,873,331, Oct. 10, 1989, Noradamantyl-carboxylic acid piperazinoalkyl esters; Wayne E. Childers, Jr., et al., 544/295, 357, 360, 394

=> d 111 ab

08 JAN 91 09:18:27

U.S. Patent & Trademark Office

P0015

JS PAT NO: 4,873,331

L11: 1 of 1

ABSTRACT:

The compounds of the following structural formula possess useful anxiolytic, antidepressant, antipsychotic and learning and memory enhancement properties:

##STR1## in which R_{sup.1} is 3-noradamantyl;

n is 0 or 1;

X is --CO.sub.2 --, --O.sub.2 C-- or --OCO.sub.2 --;

m is 1, 2, 3, 4, or 5;

and

R_{sup.2} is phenyl, benzyl, pyridinyl, pyrimidinyl, pyrazinyl or substituted phenyl or benzyl in which the substituent is alkyl, alkoxy, halo, cyano, nitro or trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

=> s adamant?
_12 3107 ADAMANT?

=> s 112 not 110
_13 2202 L12 NOT L10

=> s 113 and 19
_14 3 L13 AND L9

=> s 114 not 111
_15 3 L14 NOT L11

=> d 115 1-3

1. 4,906,779, Mar. 6, 1990, N,N'-disubstituted guanidines and their use as excitatory amino acid antagonists; Eckard Weber, et al., 564/238

08 JAN 91 09:20:35 U.S. Patent & Trademark Office P0017
2. 4,789,674, Dec. 6, 1988, Bi-2H-pyrroli(di)nediones; Romeo Paioni, 514/227.8, 232.2, 252, 316, 333, 422; 544/58.5, 141, 357, 372; 546/187, 256; 548/519

3. 4,758,575, Jul. 19, 1988, Bi-2H-pyrroli(di)nediones; Romeo Paioni, 514/316, 326, 409, 422; 544/58.5, 58.6, 111, 141, 357, 372; 546/187, 208; 548/408, 519

=> d 115 1-3 ti ab

JS PAT NO: 4,906,779 L15: 1 of 3
TITLE: N,N'-disubstituted guanidines and their use as excitatory amino acid antagonists

ABSTRACT:

Disubstituted guanidines, e.g., N,N'-di-m-tolyl guanidine, N,N'-di-o-ethylphenyl guanidine, N,N'-di-m-ethylphenyl guanidine, and

08 JAN 91 09:20:55 U.S. Patent & Trademark Office P0018

JS PAT NO: 4,906,779 L15: 1 of 3
N,N'-di-o-iodophenyl-guanidine, exhibit a high binding affinity to phenylcyclidine (PCP) receptors. These guanidine derivatives act as non-competitive blockers to glutamate induced responses of the NMDA receptor by acting as blockers for the ion channel of the NMDA receptor-ion channel complex. These compounds thus exert a neuroprotective property and are useful in the therapeutic treatment of neuronal loss in ischemia, hypoxia, hypoglycemia, and brain and spinal cord trauma as well as being useful for the treatment of epilepsy, Alzheimer's disease, Amyotrophic Lateral Sclerosis, Huntington's disease, Down's Syndrome and other neurodegenerative disorders.

JS PAT NO: 4,789,674 L15: 2 of 3
TITLE: Bi-2H-pyrroli(di)nediones
08 JAN 91 09:21:06 U.S. Patent & Trademark Office P0019

JS PAT NO: 4,789,674 L15: 2 of 3

ABSTRACT:

Novel Substituted tetrahydro-, hexahydro- and octahydro-[3,4'-bi-2H-pyrrole]-2,2'-diones of the formula ##STR1## in which each of R.sub.1 and R.sub.2 represents a carboxy-lower alkyl radical, or an unsubstituted carbamoyl-lower alkyl radical or a carbamoyl-lower alkyl radical which is N-mono- or N,N-di-substituted by lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, amino-lower alkyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, or by N,N-alkyleneamino-lower alkyl optionally substituted (in the alkyleneamino radical) by lower alkoxycarbonyl and by oxo or hydroxy, or N,N-alkylene-amino-lower alkyl optionally substituted (in

additionally by hydroxy, or N,N-(aza-, N'-lower alkylaza- or N'-lower alkanoylaza-, oxa- or thia)alkyleneamino-lower alkyl, each of which has from 4 to 8 ring members, carbamoyl-lower alkyl, N-mono- or N,N-di-lower
08 JAN 91 09:21:19 U.S. Patent & Trademark Office P0020

US PAT NO: 4,789,674 L15: 2 of 3
alkylcarbamoyl-lower alkyl, 3- to 8-membered cycloalkyl, dicycloalkyl or tricycloalkyl, or by phenyl-lower alkyl which is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, or represents a carbomoyl-lower alkyl radical which is disubstituted by alkylene optionally substituted by lower alkoxycarbonyl and by oxo or hydroxy, or by alkenylene optionally substituted by lower alkoxycarbonyl and optionally additionally by hydroxy, or by aza-, N'-lower alkylaza- or N'-lower alkanoylaza-, oxa- or thia-alkylene, each of which has from 3 to 7 chain members, each of R.sub.3, R.sub.4, R.sub.5 and R.sub.6 represents hydrogen or lower alkyl, or R.sub.3 and R.sub.4 together and/or R.sub.5 and R.sub.6 together represent a 4- to 8-membered alkylene radical, and each of R.sub.7, R.sub.8, R.sub.9 and R.sub.10 represents hydrogen, or R.sub.7 together with R.sub.8 and/or R.sub.9 together with R.sub.10 represent in each case an additional bond, and their salts, have nootropic activity and can be used as active ingredients in medicaments. They are manufactured, for
08 JAN 91 09:21:34 U.S. Patent & Trademark Office P0021

US PAT NO: 4,789,674 L15: 2 of 3
example, as follows: in a compound of the formula ##STR2## in which R'.sub.1 represents a group that can be converted into a radical R.sub.1 and R'.sub.2 represents a radical R.sub.2 or a group that can be converted into the radical R.sub.2, or in a salt thereof, R'.sub.1 is converted into a group R.sub.1 and, optionally, a radical R'.sub.2 that can be converted into R.sub.2 is converted into a group R.sub.2.

US PAT NO: 4,758,575 L15: 3 of 3
TITLE: Bi-2H-pyrroli(di)nediones

ABSTRACT:

Novel substituted tetrahydro-, hexahydro- and octahydro-[3,4'-bi-2H-pyrroli]-2,2'-diones of the formula ##STR1## in which each of R.sub.1 and R.sub.2 represents a carboxy-lower alkyl radical, or an unsubstituted carbamoyl-lower alkyl radical or a carbamoyl-lower alkyl

08 JAN 91 09:21:46 U.S. Patent & Trademark Office P0022

US PAT NO: 4,758,575 L15: 3 of 3
radical which is N-mono- or N,N-di-substituted by lower alkyl, hydroxylower alkyl, lower alkoxy-lower alkyl, amino-lower alkyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, or by N,N-alkyleneamino-lower alkyl optionally substituted (in the alkyleneamino radical) by lower alkoxycarbonyl and by oxo or hydroxy, or N,N-alkenyleneamino-lower alkyl optionally substituted (in the alkenyleneamino radical) by lower alkoxycarbonyl and optionally additionally by hydroxy, or N,N-(aza-, N'-lower alkylaza- or N'-lower alkanoylaza-, oxa- or thia)alkyleneamino-lower alkyl, each of which has from 4 to 8 ring members, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl, 3- to 8-membered cycloalkyl, dicycloalkyl or tricycloalkyl, or by phenyl-lower alkyl which is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, or represents a carbamoyl-lower alkyl radical which is disubstituted by alkylene optionally substituted by lower alkoxycarbonyl and by oxo or hydroxy, or by alkenylene optionally substituted by lower alkoxycarbonyl and optionally additionally by
08 JAN 91 09:22:01 U.S. Patent & Trademark Office P0023

US PAT NO: 4,758,575 L15: 3 of 3
hydroxy, or by aza-, N40 -lower alkylaza- or N'-lower alkanoylaza-, oxa- or thia-alkylene, each of which has from 3 to 7 chain members, each of R.sub.3, R.sub.4, R.sub.5 and R.sub.6 represents hydrogen or lower alkyl, or R.sub.3 and R.sub.4 together and/or R.sub.5 and R.sub.6 together represent a 4- to 4-membered alkylene radical, and each of R.sub.7, R.sub.8, R.sub.9 and

together with R.sub.10 represent in each case an additional bond, and their salts, have nootropic activity and can be used as active ingredients in medicaments. They are manufactured, for example, as follows: in a compound of the formula ##STR2## in which R'.sub.1 represents a group that can be converted into a radical R.sub.1 and R'.sub.2 represents a radical R.sub.2 or a group that can be converted into the radical R.sub.2, or in a salt thereof, R'.sub.1 is converted into a group R.sub.1 and, optionally, a radical R'.sub.2 that can be converted into R.sub.2 is converted into a group R.sub.2.

28 JAN 91 09:22:15

U.S. Patent & Trademark Office

P0024

US PAT NO: 4,758,575

L15: 3 of 3

LA Eng
DS CJA0AC

01/09/91

CA Structure(1st) 07/508,109

~~redone~~
redone on other search

=> file registry
COST IN U.S. DOLLARS

SINCE FILE
ENTRY
28.98

TOTAL
SESSION
29.23

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE
ENTRY
-1.36

TOTAL
SESSION
-1.36

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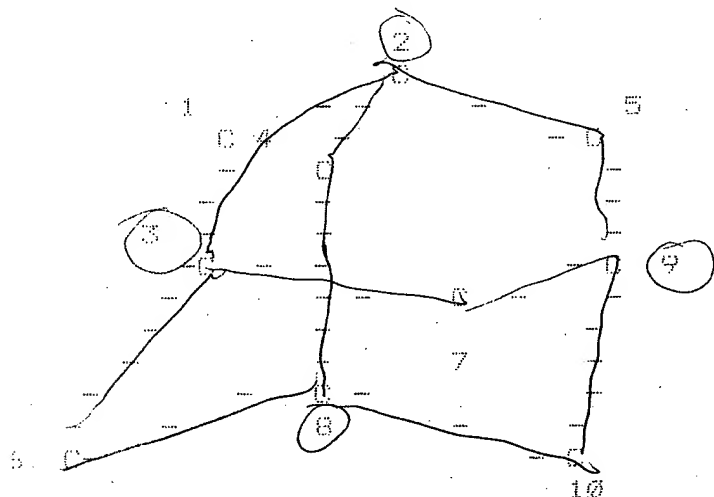
STRUCTURE FILE UPDATES: HIGHEST RN 131296-01-0

DICTIONARY FILE UPDATES: 06 JAN 91 (910106/ED) HIGHEST RN 131273-40-0

=> structure

ENTER NAME OF STRUCTURE TO BE RECALLED (NONE): adaman

ENTER (DIS), GRA, NOD, BON OR ?:



ENTER (DIS), GRA, NOD, BON OR ?:

ENTER (DIS), GRA, NOD, BON OR ? :dis

```

      13
15    G1 ----N----G1
      - 14
      -
      C
1    - - - - 5
    C 4 - 2 - C
      - C
      -
      -
18  G2 ---C - - - C ---G1 16
      - 3 - - C - - 9
      -
      8 - 7 -
      - C -
      -
6  C- - - - C
      17 G2 10
```

ENTER (DIS), GRA, NOD, BON OR ? :

ENTER (DIS), GRA, NOD, BON OR ? :dis

```

      13
15    (G1) ----N----(G1)
      - 14
      -
      C
1    - - - - 5
    C 4 - 2 - C
      - C
      -
      -
18  (G2) ---C - - - C --- (G1) 16
      - 3 - - C - - 9
      -
      8 - 7 -
      - C -
      -
6  C- - - - C
      17 (G2) 10
```

~~C++++C++++C++++C++++C~~

20 21 22 23

~~C++++C++++C++++C++++C~~

24 25 26 27 28 29

/AR (G) =H/ME/ET/I-PR/N-PR/N-BU/I-BU/S-BU/T-BU/19/24

ENTER (DIS), GRA, NOD, BON OR ? :dis sat
NODE ATTRIBUTES: NONE

GRAPH ATTRIBUTES:

~~RESP~~ 2

NUMBER OF NODES IS 27

ENTER (DIS), GRA, NOD, BON OR ? :end

L12 STRUCTURE CREATED

=> ~~sdv.11. adaman~~

=> s 112 css ful

FULL SEARCH INITIATED 9:06:14

SCREENING

FULL SCREEN SEARCH COMPLETED - 6202 TO ITERATE

23.3% PROCESSED	1444 ITERATIONS	41 ANSWERS
44.0% PROCESSED	2730 ITERATIONS	150 ANSWERS
65.1% PROCESSED	4036 ITERATIONS	246 ANSWERS
82.4% PROCESSED	5109 ITERATIONS	299 ANSWERS
93.1% PROCESSED	5773 ITERATIONS	332 ANSWERS
98.0% PROCESSED	6080 ITERATIONS	348 ANSWERS
100.0% PROCESSED	6202 ITERATIONS	350 ANSWERS

SEARCH TIME: 00.02.21

L13 350 SEA CSS FUL L12

SAU L13 adaman 2/a

=> fil ca

COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
126.40	155.63

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE ENTRY	TOTAL SESSION
0.00	-1.36

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FILE COVERS 1967 - 22 Dec 90 (901222/ED) VOL 113 ISS 26.

ALL OFFLINE Prints or Displays, use the ABS or ALL formats to obtain abstract graphic structures. The AB format DOES NOT display structure diagrams.

=> s ischemia or ischemic or ischaemia or ischaemic or hypoxia or hypoxic

11193 ISCHEMIA

3624 ISCHEMIC

24 ISCHAEMIA

31 ISCHAEMIC

8817 HYPOXIA

2173 HYPOXIC

L14 20083 ISCHEMIA OR ISCHEMIC OR ISCHAEMIA OR ISCHAEMIC OR HYPOXIA OR HYPOXIC

=> s anoxic or anoxia or stroke

1010 ANOXIC

1729 ANOXIA

934 STROKE

L15 3355 ANOXIC OR ANOXIA OR STROKE

=> s 114 or 115

L16 22669 L14 OR L15

=> s alzheimer?

=> s 117 and 113
1470 L13
L18 3 L17 AND L13

=> s 116 and 113
1470 L13
L19 3 L16 AND L13

=> s 116 and 117
L20 25 L16 AND L17

=> s 118 not 119
L21 3 L18 NOT L19

=> d 118 1-3

BIB AB

So got to
search
L13 in
CA file

Search done

Improperly; see other
newer search

L18 ANSWER 1 OF 3
COPYRIGHT (C) 1991 AMERICAN CHEMICAL SOCIETY

AN CA112(15):138764q
TI Preparation of catechol derivatives for use in disorders of central
nervous treatment
AU Fukazawa, Nobuyui; Otsuka, Kengo; Shimada, Shizuo; Miyama, Yukio;
Ikeda, Fumiaki; Kaiho, Tatsuo
CS Mitsui Toatsu Chemicals, Inc.
LO Japan
SO Eur. Pat. Appl., 22 pp.
PI EP 333522 A2 20 Sep 1989
DS R: CH, DE, FR, GB, IT, LI, NL, SE
AI EP 89-302742 20 Mar 1989
PRAI JP 88-63515 18 Mar 1988
JP 88-63516 18 Mar 1988
JP 88-201865 15 Aug 1988
JP 88-201866 15 Aug 1988
IC ICM C07C103-30
ICS A61K031-135; C07C103-26; C07D295-18; C07D207-16; C07D211-60;
A61K031-16; A61K031-19; A61K031-215; A61K031-40; A61K031-445
SC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
BX
OT (P)
CO EPXYOW
PY 1989
LA Eng

L18 ANSWER 2 OF 3
COPYRIGHT (C) 1991 AMERICAN CHEMICAL SOCIETY

AN CA109(23):207680m
TI The FMOC-ADAM approach to amino acid analysis
AU Betner, I.; Foeldi, P.
CS Pharmacia LKB Biotechnol. AB
LO Bromma S-16126, Swed.
SO LC-GC, 6(9), 832, 834, 836, 838-40
SC 9-3 (Biochemical Methods)
OT J
CO LC6CE7
IS 0888-9090
PY 1988
LA Eng

32-36

37-42

L18 ANSWER 3 OF 3
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AN CA108(11):94948p

treatment of senility
AU Goto, Giichi; Nagaoka, Akinobu; Wakimasu, Mitsuhiro
CS Takeda Chemical Industries, Ltd.
LO Japan
SO Eur. Pat. Appl., 68 pp.
PI EP 227410 A2 1 Jul 1987
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 86-309800 16 Dec 1986
PRAI JP 85-291474 24 Dec 1985
IC ICM C07K007-06
ICS A61K037-02
SC 34-3 (Amino Acids, Peptides, and Proteins)
SX 2
DT P
CO EPXXDW
PY 1987
LA Eng

=> d 118 1-3 ti ab

_118 ANSWER 1 OF 3

COPYRIGHT (C) 1991 AMERICAN CHEMICAL SOCIETY

TI Preparation of catechol derivatives for use in disorders of central nervous treatment
4B Title compds. I (R1 = H, Ac; R2 = R3R4NCO, Q, R6R7N, CO2R8; R3, R4 = H, alkyl, cycloalkyl, (un)substituted aryl; R5 = H, alkyl (un)substituted aryl, alkoxy carbonyl; X = bond, O, N, CH2; R6, R7 = H, alkyl, alkanoyl; R8 = H, alkyl; n = 1-3; (R1 = R6 = R7 = H and n = 2) and (R1 = R6 = H, R7 = Me, and n = 2) are excluded.], useful for treatment of regressive disorders of central nervous system including senile dementia of the Alzheimer type, are prepd. I also produce nerve growth factor (NGF) in particular tissues of the brain. Dihydrocaffeic acid in EtOH was refluxed in the presence of H2SO4 for 3 h to give 3,4-(HO)2C6H3CH2CH2CO2Et, to which in pyridine was added Ac2O to give I (R1 = Ac; R2 = CO2Et; n = 2). In test for promoting activity for prodn. and secretion of NGF in mouse cells, I (R1 = Ac; R2 = AcNH) at 0.2 mM showed a NGF increase ratio of 12.21.

_118 ANSWER 2 OF 3

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TI The FMOC-ADAM approach to amino acid analysis
4B Manual and automatic amino acid anal. by HPLC using automated precolumn derivatization with 9-fluorenylmethoxycarbonyl chloride (FMOC) and 1-aminoadamantane (ADAM) is described. Confirmatory expts. are presented, such as studies of reproducibility (CV values in the femtomole range). The limitations of the method are discussed, esp. with respect to the sensitivity, which is .apprx.50 fmol. Results are presented for analyses of protein hydrolyzate samples from Notochis II (a protein isolated from an Australian snake) and from victims of Alzheimer's disease.

_118 ANSWER 3 OF 3

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TI Preparation of vasopressin fragment derivatives as nootropics for treatment of senility
4B PGIu-Asp(NHR1)-Cys(H-Cys-OH)-A-D-Lys-B [I; R1 = H, C1-18 alkyl, (substituted) phenyl-C1-3 alkyl; A = amino, C1-6 alkylamino acid residue; B = OH, amino, amino acid or amide] were prepd. as vasopressin fragment peptides, useful for treatment and prevention of dementia. PGIu-Asn-Cys(H-Cys-OH)-Pro-D-Lys-OH (II) was prepd. using soln.-phase methods, starting from BOC-D-Lys(Z)-OH.DCHA (BOC = tert-butyloxycarbonyl, Z = benzyloxycarbonyl, DCHA =

mice when given intracerebroventricularly at 10 pg-10 ng.

=> d 119 1-3

L19 ANSWER 1 OF 3

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AN CA113(21):104614j
TI Neuroprotective effect of memantine demonstrated in vivo and in vitro
AU Seif el Nasr, Mona; Peruche, Barbara; Rossberg, Christine; Mennel, Hans Dieter; Kriegstein, Josef
CS Inst. Pharmakol. Toxikol., Philipps-Univ.
LO Marburg D-3550, Fed. Rep. Ger.
SO Eur. J. Pharmacol., 185(1), 19-24
SC 1-11 (Pharmacology)
DT J
CO EJPHAZ
IS 0014-2999
PY 1990
LA Eng

L19 ANSWER 2 OF 3

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AN CA112(19):174876m
TI Amantadine and derivatives as modifiers of x-rays on mammalian cells
AU Alvarez, M. V.; Izquierdo, M. C.
CS Ist. Quim. Fis. "Rocasolano", CSIC
LO Madrid 28006, Spain
SO An. Quim., Ser. C, 85(1), 113-15
SC 8-6 (Radiation Biochemistry)
DT J
CO AQSB06
IS 0211-1357
PY 1989
LA Span

L19 ANSWER 3 OF 3

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AN CA94(11):76956c
TI Dopaminergic agonists and conditioned avoidance response in normoxic or hypoxic rats
AU Saligaut, Christian; Moore, Nicholas; Leclerc, Jean Luc; Boismare, Francis
CS Dep. Pharmacol., Hotel-Dieu
LO Rouen 76031, Fr.
SO Aviat., Space Environ. Med., 52(1), 19-23
SC 1-5 (Pharmacodynamics)
DT J
CO ASEM06
IS 0095-6562
PY 1981
LA Eng

=> d 119 1-3 ti ab

L19 ANSWER 1 OF 3

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TI Neuroprotective effect of memantine demonstrated in vivo and in vitro
AB The protective effects of the anticonvulsant memantine against hypoxic or ischemic damage were studied in a rat model of transient

hemispheres. Ischemia was induced for 10 min by clamping both arteries and lowering the mean arterial blood pressure to 40 mmHg; the rats were allowed to recover for 7 days. Cultured neurons were made hypoxic with 1 mM NaCN added to the incubation medium for 30 min followed by a recovery period of 3 days. The effects of memantine were compared with those produced by a typical non-competitive N-methyl-D-aspartate antagonist, dizocilpine. Similar effects were obtained with both drugs. The drugs reduced the damage caused by transient ischemia to neurons of the hippocampal CA1 subfield. Memantine (10 and 20 mg/kg) had a dose-dependent effect when administered i.p. to rats 1 h before ischemia. Dizocilpine was active at 1 mg/kg. When administered after ischemia, 10 mg memantine/kg protected CA1 neurons against ischemic damage. The 2 drugs protected cultured neurons against hypoxic damage. The lowest effective concn. was 0.1 μ M dizocilpine and 1 μ M memantine. Thus, memantine possesses neuroprotective activity but is less potent than dizocilpine.

L19 ANSWER 2 OF 3

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TI Amantadine and derivatives as modifiers of x-rays on mammalian cells
 AB The x-ray modifying effects of amantadine (I) and 2 of its derivs. [1-adamantyl-4-nitropyrazole (II) and 1-(3-hydroxy-1-adamantyl)-4-nitropyrazole (III)] were studied in hamster tumor cell cultures under oxic and hypoxic conditions. I showed a moderate radiosensitizing effect under hypoxic conditions whereas II had no radiomodifying effect. III exhibited a radiosensitizing effect under hypoxic conditions even in the presence of the radioprotectant DMSO. The radiosensitizing effect was attributed to the presence of the (OH group).

L19 ANSWER 3 OF 3

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TI Dopaminergic agonists and conditioned avoidance response in normoxic or hypoxic rats
 AB The actions of 4 dopaminergic agonists, apomorphine [58-00-4], bromocriptine [25614-03-3], amantadine [768-94-5], piribedil [3605-01-4] on a conditioned avoidance response were studied in normoxic or hypobaric hypoxic rats. Low doses of agonists have no effects in normoxia, but induce an antihypoxic protection. (Improvement of learning in hypoxia). In contrast, the higher doses impair learning both in normoxia and hypobaric hypoxia. The possibility of an antihypoxic property induced by dopaminergic postsynaptic receptors stimulation is discussed and seems to be the main phenomenon whereas action on other nonspecific sites seems to be responsible for the high dose-induced impairment of learning and of resistance to hypoxia.

=> s 120 not 119

L22 25 L20 NOT L19

=> s 120 not 118

L23 25 L20 NOT L18

=> d 123 1-25

L23 ANSWER 1 OF 25

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AN CA113(21):104729a

TI Preparation of arylamides for treatment of mental disorders

AU Usherwood, Peter Norman Russell; Bycroft, Barrie Walsham;

Blagbrough, Ian Stuart; Mather, Alan John

LQ UK
SO PCT Int. Appl., 36 pp.
PI WO 9002114 A1 8 Mar 1990
DS W: AU, DK, JP, US
AI WO 89-081004 30 Aug 1989
PRAI GB 88-20442 30 Aug 1988
IC ICM C07C235-34
ICS A61K031-16; A61K031-165; C07C235-50; C07C235-60
SC 1-11 (Pharmacology)
SX 25
DT P
CO PIXXD2
PY 1990
LA Eng

L23 ANSWER 2 OF 25

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AN CA113(18):158675k
TI Dihydroxycinnamic acid amide derivatives and their pharmaceutical compositions for enhancement of nerve growth factor (NGF) production
AU Kishimoto, Toshimitsu; Ono, Takashi; Okumoto, Takeki; Arita, Masafumi
CS Yoshitomi Pharmaceutical Industries, Ltd.
LO Japan
SO Jpn. Kokai Tokkyo Koho, 9 pp.
PI JP 02104568 A2 17 Apr 1990 Heisei
AI JP 89-158541 21 Jun 1989
PRAI JP 88-153839 22 Jun 1988
IC ICM C07C235-34
ICS A61K031-165; A61K031-215; A61K031-40; A61K031-445; A61K031-495; A61K031-55; C07D207-09; C07D211-18; C07D223-04; C07D223-12; C07D227-04; C07D227-10; C07D295-18
SC 63-5 (Pharmaceuticals)
SX 2
DT P
CO JKXXAF
PY 1990
LA Japan

L23 ANSWER 3 OF 25

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AN CA113(17):145350a
TI Treatment of neuropsych disorders with cyclopropanecarboxylates
AU Skolnick, Phil; Lewin, Anita; Marvizon, Juan Carlos; Monn, James; Rice, Kenner
CS National Institutes of Health
LO USA
SO U. S. Pat. Appl., 35 pp. Avail. NTIS Order No. PAT-APPL-7-390 745.
PI US 390745 A0 15 Jan 1990
AI US 89-390745 8 Aug 1989
SC 1-11 (Pharmacology)
DT P
CO XAXXAV
PY 1990
LA Eng

L23 ANSWER 4 OF 25

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AN CA113(9):78420h
TI Preparation and formulation of (tetrazolylalkyl)piperazinecarboxylic acid as excitatory amino acid receptor antagonists
AU Ornstein, Paul L.

LD USA
SD U.S., 7 pp.
FI US 4902687 A 20 Feb 1990
AI US 89-328348 27 Mar 1989
IC ICM A61K031-495
ICS C07D403-06; C07D403-14
NCL 514253000
SC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 63
DT P
CO USXXAM
PY 1990
LA Eng

L23 ANSWER 5 OF 25

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AN CA113(9):77927s
TI Preparation of N,N'-disubstituted guanidines as excitatory amino acid antagonists
AU Weber, Eckard; Keana, John F.
CS Oregon Health Sciences University
LD USA
SD U.S., 11 pp. Cont.-in-part of U.S. Ser. No. 1,545.
FI US 4906779 A 6 Mar 1990
AI US 86-237367 29 Aug 1988
PRAI US 86-884150 10 Jul 1986
US 87-1545 26 Jun 1987
IC ICM C07C129-12
NCL 544238000
SC 25-21 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
SX 1
DT P
CO USXXAM
PY 1990
LA Eng

L23 ANSWER 6 OF 25

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AN CA113(5):40474r
TI Preparation and formulation of 6-(acylmethyl)decahydroisquinoline-1- or -3-carboxylates as excitatory amino acid neurotransmitter antagonists
AU Ornstein, Paul L.
CS Lilly, Eli, and Co.
LD USA
SD U.S., 11 pp.
FI US 4902695 A 20 Feb 1990
AI US 89-309562 13 Feb 1989
IC ICM A61K031-47
ICS C07D215-14; C07D215-36
NCL 514307000
SC 27-17 (Heterocyclic Compounds (One Hetero Atom))
SX 1, 29, 63
DT P
CO USXXAM
PY 1990
LA Eng

L23 ANSWER 7 OF 25

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AN CA113(1):6150x
TI Preparation of aminoalkylpyrroles as CNS agents

CS Cassella A.-G.
LO Fed. Rep. Ger.
SO Ger. Offen., 17 pp.
PI DE 3820190 A1 21 Dec 1989
AI DE 88-3820190 14 Jun 1988
IC ICM C07D207-34
ICS C07D403-00; C07D207-42; C07D207-335; C07D207-337; C07D417-12;
C07D417-06; A61K031-40; A61K031-415; A61K031-425; A61K031-55;
C07D521-00
ICI C07D207-30, C07D333-04, C07D227-00, C07D309-00, C07D313-02,
C07D337-02, C07D247-00; C07D207-30
SC 27-10 (Heterocyclic Compounds (One Hetero Atom))
SX 1
DT P
CO GWXXBX
PY 1989
LA Ger

L23 ANSWER 8 OF 25

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AN CA112(25):235290q
TI Preparation of 1,3-disubstituted pyrrolidines as serotonin (partial)
agonists and antagonists
AU Schohe, Rudolf; Seidel, Peter Rudolf; Traber, Jorg; Glaser, Thomas
CS Bayer A.-G.
LO Fed. Rep. Ger.
SO Eur. Pat. Appl., 50 pp.
PI EP 338331 A1 25 Oct 1989
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, NL, SE
AI EP 89-106023 6 Apr 1989
PRAI DE 88-3812989 19 Apr 1988
DE 88-3835271 15 Oct 1988
IC ICM C07D417-06
ICS C07D401-06; C07D207-12; C07D207-08; C07D207-09; C07D405-06;
C07D403-12; A61K031-40; A61K031-41; A61K031-44
SC 26-7 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1
DT P
CO EPXXDW
PY 1989
LA Ger

L23 ANSWER 9 OF 25

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AN CA112(19):178657p
TI Preparation of 1,3,4,5-tetrahydrobenzic,dlindoles as drugs
AU Junge, Bodo; Richter, Bernd; Glaser, Thomas; Traber, Joerg
CS Bayer A.-G.
LO Fed. Rep. Ger.
SO Eur. Pat. Appl., 50 pp.
PI EP 332968 A1 20 Sep 1989
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 89-103071 6 Mar 1989
PRAI DE 88-3809155 18 Mar 1988
IC ICM C07D417-12
ICS C07D209-90; C07D401-12; C07D403-12; A61K031-40; A61K031-425
SC 27-10 (Heterocyclic Compounds (One Hetero Atom))
SX 1
DT P
CO EPXXDW
PY 1989
LA Ger

AN CA112(13):118825g
TI Preparation and formulation of tetrazole excitatory amino acid
receptor antagonists for treatment of nervous system disorders
AU Ornstein, Paul Leslie
DS Lilly, Eli, and Co.
LO USA
SO Eur. Pat. Appl., 25 pp.
PI EP 330353 A1 30 Aug 1989
OS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 89-301337 13 Feb 1989
PRAI US 88-157760 19 Feb 1988
IC ICM C07D401-06
ICS A61K031-445; A61K031-41
ICI C07D401-06, C07D257-00; C07D211-00
SC 26-10 (Heterocyclic Compounds (More Than One Hetero Atom))
BX 1, 63
DT P
DO EPXXDW
PY 1989
LA Eng

_23 ANSWER 11 OF 25

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AN CA112(4):25677v
TI Axon-regenerating agents containing phosphatidylinositol,
phosphatidylcholine, phosphatidylserine, and/or sphingomyelin
AU Arakawa, Yoshihiro; Tachibana, Shinro
DS Eisai Co., Ltd.
LO Japan
SO Jpn. Kokai Tokkyo Koho, 4 pp.
PI JP 01135720 A2 29 May 1989 Heisei
AI JP 87-291783 20 Nov 1987
IC ICM A61K031-685
ICS A61K031-685
SC 63-6 (Pharmaceuticals)
BX 1
DT P
DO JKXXAF
PY 1989
LA Japan

_23 ANSWER 12 OF 25

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AN CA111(17):151441f
TI Development and selective neurodegeneration in cell cultures from
different hippocampal regions
AU Mattson, Mark P.; Kater, S. B.
DS Dep. Anat. Neurobiol., Colorado State Univ.
LO Fort Collins, CO 80523, USA
SO Brain Res., 490(1), 110-25
SC 14-10 (Mammalian Pathological Biochemistry)
DT J
DO BRREAP
IS 0006-8973
PY 1989
LA Eng

_23 ANSWER 13 OF 25

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AN CA111(9):78023q

production, and cerebral dysfunction remedy comprising it as active ingredient
AU Iemura, Ryuichi; Hori, Manabu; Ohtaka, Hiroshi; Sukamoto, Takayuki;
Hara, Hideaki; Ito, Keizo
CS Kanebo, Ltd.
LO Japan
SO Eur. Pat. Appl., 19 pp.
PI EP 302967 A2 15 Feb 1989
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-118691 16 Dec 1987
PRAI JP 87-200510 10 Aug 1987
IC ICM C07D239-95
ICS A61K031-505
SC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 63
DT F
CU EPXXDW
FY 1989
LA Eng

L23 ANSWER 14 OF 25

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AN CA111(9):78020m
TI Preparation of pharmaceutically active heterocyclic amines and their
use for treating head injury, spinal trauma, stroke, etc.
AU McCall, John M.; Ayer, Donald E.; Jacobsen, E. Jon; Van Doornik,
Frederick J.; Palmer, John R.
CS Upjohn Co.
LO USA
SO PCT Int. Appl., 173 pp.
PI WO 8808424 A1 3 Nov 1988
DS W: AU, DK, FI, JP, KR, NO, US
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE
AI WO 88-US1212 20 Apr 1988
PRAI US 87-43274 27 Apr 1987
IC ICM C07D401-14
ICS C07D239-50; C07D213-74; C07D405-12; C07D405-14; C07D251-40;
C07D251-70; C07D267-14; C07D265-14; A61K031-35
SC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 25, 27
DT F
CU PIXXD2
FY 1988
LA Eng

L23 ANSWER 15 OF 25

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AN CA111(3):23387f
TI Preparation of 3-indolepyruvic acid derivatives and pharmaceutical
use thereof
AU De Luca, Giovanna; Di Stazio, Giovanni; Margonelli, Andrea;
Materazzi, Mario; Politi, Vincenzo
CS Polifarma S.p.A.
LO Italy
SO PCT Int. Appl., 26 pp.
PI WO 8809759 A2 15 Dec 1988
DS W: AU, BR, DK, FI, JP, KR, NO, US
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE
AI WO 88-IT41 1 Jun 1988
PRAI IT 87-48014 3 Jun 1987
IC ICM C07D209-18
ICS A61K031-405
SC 27-11 (Heterocyclic Compounds (One Hetero Atom))

DT P
DO FIXXD2
PY 1988
LA Eng

L23 ANSWER 16 OF 25

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AN CA110(15):135273b
TI Preparation of substituted imidazolylalkylpiperazines and
-diazepines as pharmaceuticals
AU Pascal, Jean Claude; Lee, Chi Ho; Alps, Brian J.; Pinhas, Henri;
Whiting, Roger L.; Beranger, Serge
CS Syntex Pharmaceuticals Ltd.
LO UK
BO Eur. Pat. Appl., 44 pp.
PI EP 289227 A1 2 Nov 1988
OS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 88-303646 22 Apr 1988
PRAI US 87-42181 24 Apr 1987
IC ICM C07D233-64
ICS C07D403-06; A61K031-415; A61K031-435
SC 28-21 (Heterocyclic Compounds (More Than One Hetero Atom))
BX 1, 63
OT P
DO EPXXDW
PY 1988
LA Eng

L23 ANSWER 17 OF 25

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AN CA110(11):88637m
TI Method and compositions containing enantiomer of analgesic opioid
agonist or antagonist for reducing neurotoxic injury
AU Choi, Dennis W.
CS Leland Stanford Junior University
LO USA
BO Eur. Pat. Appl., 8 pp.
PI EP 270290 A2 8 Jun 1988
OS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-310323 23 Nov 1987
PRAI US 86-934733 25 Nov 1986
IC ICM A61K031-485
SC 1-11 (Pharmacology)
OT P
DO EPXXDW
PY 1988
LA Eng

L23 ANSWER 18 OF 25

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AN CA110(1):893h
TI Treatment of cerebral disorder and skin disease by
1,3-dibutyl-7-(2-oxypropyl)xanthine
CS Beecham Group PLC
LO UK
BO Jpn. Kokai Tokkyo Koho, 6 pp.
PI JP 63079832 A2 9 Apr 1988 Showa
AI JP 87-227523 10 Sep 1987
PRAI GB 86-21869 11 Sep 1986
IC ICM A61K031-52
ICS A61K031-52
ICA C07D473-06

DT P
CO JKXXAF
PY 1988
LA Japan

L23 ANSWER 19 OF 25

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AN CA109(21):190425g
TI Preparation of 5-aryl-3H-1,2,4-triazol-3-ones and their use in the treatment of neurodegenerative disorders
AU Miller, Francis P.; Kane, John M.; Sorensen, Stephen
CS Merrell Dow Pharmaceuticals, Inc.
LO USA
SO Eur. Pat. Appl., 10 pp.
PI EP 273309 A2 6 Jul 1988
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-118727 17 Dec 1987
PRA1 US 86-944634 19 Dec 1986
US 87-107001 16 Oct 1987
IC ICM A61K031-41
ICS A61K031-44; A61K031-47
SC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
BX 1
DT P
CO EPXXDW
PY 1988
LA Eng

L23 ANSWER 20 OF 25

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AN CA109(9):73258u
TI Xanthine derivatives, their preparation and pharmaceutical compositions containing them
AU Nicholson, Charles David; Goering, Joachim; Morgan, Brian; Arch, Jonathan Robert Sanders
CS Beecham-Wuelting G.m.b.H. und Co. K.-G.; Beecham Group PLC
LO Fed. Rep. Ger.
SO Eur. Pat. Appl., 19 pp.
PI EP 260127 A2 16 Mar 1988
DS R: BE, CH, DE, FR, GB, IT, LI, NL
AI EP 87-307978 9 Sep 1987
PRA1 GB 86-21870 11 Sep 1986
IC ICM C07D473-04
ICS A61K031-52
SC 26-9 (Biomolecules and Their Synthetic Analogs)
BX 1
DT P
CO EPXXDW
PY 1988
LA Eng

L23 ANSWER 21 OF 25

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AN CA108(23):204482s
TI Preparation of pyridol[1,2-a]indoles for treatment of cerebrovascular disorders
AU Thielke, Dietrich; Hoeltje, Dagmar; Nadler, Guy
CS Beecham-Wuelting G.m.b.H. und Co. K.-G.; Laboratoires Sobio S. A.
LO Fed. Rep. Ger.
SO Eur. Pat. Appl., 22 pp.
PI EP 252643 A1 13 Jan 1988
DS R: BE, CH, DE, FR, GB, IT, LI, NL

FRAT GB 86-16031 1 Jul 1986
GB 86-30634 22 Dec 1986
IC ICM C07D471-04
ICS A61K031-435
ICI C07D471-04, C07D221-00, C07D209-00
SC 27-10 (Heterocyclic Compounds (One Hetero Atom))
SX I
DT P
CO EPXXDW
PY 1988
LA Eng

_23 ANSWER 22 OF 25

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AN CA107(7):54931a
TI Determination of regional glucose metabolism in brain by FDG and PET with reference to drug effects and changes in the course of cerebrovascular disease and dementia
AU Heiss, W. D.; Herholz, K.; Pawlik, G.; Beil, C.; Dal-Bianco, P.; Szekely, B.; Wienhard, K.
CS Max-Planck-Inst. Neurol. Forsch.
LO Cologne 5000/9; Fed. Rep. Ger.
BD Pharmacol. Cereb. Ischemia, Proc. Int. Symp., 87-98. Edited by: Kriegstein, Josef. Elsevier: Amsterdam, Neth.
SC 8-9 (Radiation Biochemistry)
SX 1, 14
DT C
CO 55RKAB
PY 1986
LA Eng

_23 ANSWER 23 OF 25

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AN CA106(21):174037q
TI Dysfunction of central cholinergic system in hyperkinetic rats, following postnatal anoxia
AU Speiser, Zipora; Sharafan, Chen; Gitter, Simon; Cohen, Sasson; Gonen, Baruch; Rehavi, Moshe
CS Sackler Fac. Med., Tel Aviv Univ.
LO Tel Aviv 69978, Israel
BD Adv. Behav. Biol., 29(Alzheimer's Parkinson's Dis.), 487-94
SC 14-10 (Mammalian Pathological Biochemistry)
DT J
CO ADBREW
IS 0079-6246
PY 1986
LA Eng

_23 ANSWER 24 OF 25

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AN CA104(13):107124m
TI Phosphorus-31 nuclear magnetic resonance studies of anoxia and ischemia in animal brain and of human brain in Alzheimer's and Huntington's diseases
AU Cohen, M. M.; Kopp, S. J.; Pettegrew, J. W.; Minshew, N.; Kriegstein, J.; Glonek, T.
CS Rush-Presbyterian St. Lukes Med. Cent.
LO Chicago, IL, USA
BD Mal. Med./Drugs Dis., 1(3), 85-90
SC 14-0 (Mammalian Pathological Biochemistry)
DT J
CO MMDDDB

LA Eng

L23 ANSWER 25 OF 25

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AN CA102(17):146651j
TI Biological plasticity of the aging brain
AU Hoyer, Siegfried
CS Dep. Pathochem. Gen. Neurochem., Univ. Heidelberg
LO Heidelberg D-6900, Fed. Rep. Ger.
SO Top. Aging Res. Eur., 2(Aging Brain Senile Dementia), 23-42
SC 13-3 (Mammalian Biochemistry)
SX 14
DT J
CO TAEUEN
PY 1984
LA Eng

=> d 123 1-25 ti ab

L23 ANSWER 1 OF 25

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TI Preparation of arylamides for treatment of mental disorders
AB The title compds.
 $Aa(C_6H_5-a)XbCONH(CH_2)cND(CH_2)dNE(CH_2)e[NY(CH_2)h]iNGJ$ [A = OH, alkoxy, cycloalkoxy, acyloxy, halo, etc.; a = 0-5; Y = Cl-6 (un)substituted aliph. hydrocarbyl; b = 0, 1; c, d, f, h = 2-6; i = 0, 1; D, E, Y = H, Cl-C4 alkyl, cycloalkyl; G, J, N = heterocyclyl] are effective for the treatment of cerebral disorders, such as psychosis, senile dementia, and ischemia. To a soln. of 4-hydroxyphenylacetic acid in 1,2-dimethoxyethane (DME) was added a soln. of dicyclohexyl carbodiimide in DME and left at 25.degree. for 3 h. The ppt. was filtered and the filtrate and the washings were combined and a soln. of spermine was added and sealed under an atm. of N and allowed to stand at 25.degree. for 48 h and then concd. The residue was purified with column chromatog. and lyophilized to give N-(hydroxyphenylacetyl)spermine (I). The potency of I was tested as an antagonist of N-methyl-D-aspartate (NMDA)- and (RS)-.alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)- induced response in a rat brain slice model. I at 10⁻⁵M decreased electrophysiol. recorded depolarization responses by 22% for AMPA-induced one and 35% for NMDA-induced one from the control level.

L23 ANSWER 2 OF 25

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TI Dihydroxycinnamic acid amide derivatives and their pharmaceutical compositions for enhancement of nerve growth factor (NGF) production
AB Pharmaceutical compns. contg. dihydroxycinnamic acid amides [I; R1, R2 = H, alkyl, acyl, aralkyl; R3, R4 = H, alkyl, aralkyl, G; R5 = H, alkyl, cycloalkyl, (halo-, alkyl-, alkoxy-, and CF3-substituted) aryl, aralkyl, or aryloxyalkyl; m = 0-4; n = 1-3; or NR3R4 = heterocyclyl contg. G, S, or (substituted) NH] or their pharmaceutically acceptable acid addn. salts are useful for treatment and prophylaxis of central nervous system diseases or prevention of the progress of nerve cell disorders, e.g. Alzheimer's disease, senile dementia, or ischemic brain disorders. Eleven I in vitro stimulated 1.53 +/- 0.07 to 3.43 +/- 0.04 times the nerve growth factor prodn. in mouse fibroblastoma L-M cells as compared to that of the control. Generic tablet and capsule formulations contg. I are described.

L23 ANSWER 3 OF 25

TI Treatment of neuropsychic disorders with cyclopropanecarboxylates
AB The cyclopropanecarboxylates I [A = (un)substituted NH₂; B = OH, OR₁; R₁ = substituted alkyl] and pharmaceutical salts thereof are drugs for the treatment of neuropsychopharmacol. disorders, assocd. with activation of the N-methylaspartate (NMDA) receptor complex. I are partial agonists of the strychnine-insensitive glycine modulatory site of the NMDA receptor complex. I (A = NH₂, B = OH) (400 mg/kg) protected mice against convulsions induced by 125 mg NMDA/kg.

23 ANSWER 4 OF 25

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TI Preparation and formulation of (tetrazolylalkyl)piperazinecarboxylic acid as excitatory amino acid receptor antagonists
AB The title compds. II; R₁ = CO₂H, COR₃, CONR₄2, SO₂R₃, etc.; R₂ = H, C₁-4 alkyl, (Ph)C₁-4 alkyl; R₃ = C₁-16 alkoxy, (Ph)C₁-4 alkoxy, etc.; R₄ = H, C₁-16 alkyl, (Ph)C₁-4 alkyl, Ph; n = 2, 3] or their pharmaceutically acceptable salts, useful for treatment of epilepsy, stroke, anxiety, cerebral ischemia, muscular spasms, Alzheimer's disease, and Huntington's disease, were prepd. Pyrazinamide was hydrogenated over PtO₂ and the resulting piperazine analog was N-alkylated by 4-bromobutyronitrile in EtOH, in the presence of Hunig's base and then treated with di-tert-Bu carbonate to give N-protected cyanopropylpiperazine II. Heating of II for 4 days at 80.degree. with Bu₃SnN₃ under N gave the appropriate tetrazole deriv. which was deprotected and the carbamoyl group hydrolyzed to give the title compd. I (R₁ = CO₂H, R₂ = R₄ = H, n = 3) (III) which in rats inhibited seizures induced by N-methyl-D-aspartate with a min. ED (MED) of 100 mg/kg. An analog of III (n = 2) had min. ED of 20 mg/kg in the same expt. Pharmaceuticals comprising I are given.

23 ANSWER 5 OF 25

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TI Preparation of N,N'-disubstituted guanidines as excitatory amino acid antagonists
AB RNHC(=NH)NHR₁ II; R, R₁ = (un)substituted alkyl, cycloalkyl, aryl, aralkyl] were prepd. as methylaspartate receptor ion-channel blockers useful as neuroprotective agents for treatment of, e.g., Alzheimer's disease. Thus, 3-EtC₆H₄NH₂ was heated 15 min at 150.degree. with BrCN to give 20% I (R = R₁ = 3-EtC₆H₄) which had IC₅₀ of 168 and 52 nM against MK-801 and 1-[1-(2-thienyl)cyclohexyl]piperidine binding to rat brain membrane, resp.

23 ANSWER 6 OF 25

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TI Preparation and formulation of
6-(acylmethyl)decahydroisoquinoline-1- or -3-carboxylates as excitatory amino acid neurotransmitter antagonists
AB The title compds. II; X = CO₂H, COR₃, CONR₂4, CONHSO₂R₄, CONHCOR₃, SO₂R₃, P(O)(OR₄)₂, tetrazolyl group Q; R₃ = alkoxy, phenylalkyloxy, (un)substituted PhCH₂O, alkanoyloxymethyl; R₄ = H, alkyl, Ph, phenylalkyl; 1 of Y, Z = H, the other = CO₂H, COR₃, CONR₂4, CONHSO₂R₄, CONHCOR₃, Q] were prepd. Thus, 4-HOC₆H₄CH₂CH(NH₂)CO₂H was cyclocondensed with HCHO and the product converted in 4 steps to isoquinolinocarboxylate II (R = CO₂Me, R₁R₂ = O, R₅ = Et, which was refluxed 6 h in THF with [(EtO)₂P(O)]₂CH₂ which had been treated with NaH to give II [R, R₅ as above, R₁R₂ = CH₂P(O)(OEt)₂]. The latter was hydrogenated and the product deprotected to give II [R = R₂ = R₅ = H, R₁ = CH₂P(O)(OH)₂] which had min. ED of 5 mg/kg i.p. for prevention of N-methyl-D-aspartate-induced seizures in neonatal

1989
 TI Preparation of aminoalkylpyrroles as CNS agents

AB The title compds. II; R₁, R₂ = H, alkyl; R₃ = H, alkyl, (modified) carboxylate; R₄ = (modified) carboxylate, NO₂, alkylsulfinyl, alkylsulfonyl, (substituted) phenylsulfinyl, phenylsulfonyl, PhCO, alkylcarbonyl, F₃CCO, (NC)₂CH, heterocycliccarbonyl; R₅ = aminoalkyl, acylaminoalkyl, were prepd. as nootropics (no data). Thus, MeCOCH₂CO₂Me was added slowly to AcNHCH₂CH₂NH₂. ClCH₂CO₂Me was added and the mixt. was refluxed 20 h to give 44% pyrrolecarboxylate II.

TI Preparation of 1,3-disubstituted pyrrolidines as serotonin (partial) agonists and antagonists

AB The title compds. II; A = (fused) heteroaryl; B = cyano, CO₂R₁, CONR₂R₃, SO₂NR₂R₃, SO₂R₄, NR₅R₆, C.tpi bond. COCH₂NR₅R₆; X = OCH₂, CH₂O, O; R₁ = H, C1-12 alkyl, C5-8 cycloalkyl, C2-12 alkenyl, aryl, aralkyl; R₂, R₃ = H, C1-17 alkyl, (un)substituted aryl, etc.; R₅, R₆ = COR₂, SO₂R₈, any of definitions for R₂, R₃; R₇ = NHR₉, C1-12 alkyl, C1-17 alkoxy, etc.; R₈ = C5-8 cycloalkyl, (un)substituted C1-12 alkyl, (un)substituted (hetero)aryl, NR₂R₃; R₉ = H, C5-8 cycloalkyl, (un)substituted C1-12 alkyl, aralkyl, (hetero)aryl, etc.; NR₅R₆ can form a (fused) heterocyclic ring, e.g., Q1, Q2, etc.; n = 1-10; n = 0-21 and their salts were prepd. as 5-hydroxytryptamine agonists, partial agonists (no data), and antagonists, useful for treatment of serotoninergic system-related CNS diseases. A mixt. of 3-(2-cyanophenoxy)pyrrolidine, 2-(4-bromobutyl)benzothiazol-3(2H)-one-1,1-dioxide, and Et₃N in DMF was stirred 20 h at 45.degree. to give II which was converted to its oxalate. The latter in vitro antagonized serotonin with an inhibition const. K_i = 2 nM.

TI Preparation of 1,3,4,5-tetrahydrobenzic,d,lindoles as drugs

AB The title compds. II; R₁ = H, alkyl, aralkyl, heteroarylalkyl; X = H, OMe, OH, SMe, halo, cyano, CONH₂; Y = alkylene; Z = cyano, NR₂R₃, OR₄, SO₂R₅, CO₂R₆, CONR₇R₈; R₂, R₃ = H, (cyclo)alkyl, alkenyl, (substituted) aryl, aralkyl, COR₉, SO₂R₁₀; R₂R₃ = Q1, Q2, Q3, etc.; R₄ = H, (cyclo)alkyl, alkenyl, aryl, aralkyl, acyl, alkoxycarbonyl, etc.; R₅ = (cyclo)alkyl, alkenyl, (substituted) aryl, aralkyl, NR₇R₈; R₆ = H, (cyclo)alkyl, alkenyl, aryl, aralkyl; R₇, R₈ = H, R₆; R₉ = H, amino, alkyl, alkoxy, (substituted) aryl, aralkyl, aralkoxy, heteroaryl; R₁₀ = (substituted) alkyl, aryl, aralkyl, heteroaryl, NR₇R₈; m = 0-21, useful as central nervous system agents, were prepd. Thus, 6-methoxy-4-amino-1,3,4,5-tetrahydrobenzic,d,lindole and Et₃N in DMF were treated dropwise with 2-(4-bromobutyl)-1,2-benzisothiazol-3(2H)-one 1,1-dioxide in DMF and the mixt. was stirred 4 h at 50.degree. to give I [R₁ = H, X = OMe, Y = (CH₂)₄, Z = Q1]. I bound to 5 HT₁ receptors with IC values of 0.7-0.9 nmol/L. Several I showed antidepressant activity.

TI Preparation and formulation of tetrazole excitatory amino acid receptor antagonists for treatment of nervous system disorders

AB The title compds. (I); R₁ = CO₂R₃, CONR₄2, CONHSO₂R₃, CONHCOR₃, O; R₂ = H, C1-3 alkyl; n = 0-3; m = 0; i; m + n = 0-3; R₃ = H, C1-4 alkyl,

which are antagonists of excitatory amino acid receptors and thereby useful for the treatment of neural disorders (e.g. epilepsy, stroke, and anxiety) and neurodegenerative disorders such as Alzheimer's disease and Huntington's disease, are prepd. Thus, bromination of Me cis-4-(2-hydroxyethyl)-N-tert-butoxycarbonyl-2-piperidinecarboxylate with Ph3PBr2 in CH2Cl2 followed by cyanation with NaCN in DMSO gave Me cis-4-(2-cyanoethyl)-N-butoxycarbonyl-2-piperidinecarboxylate which was heated 48 h at 80.degree. with Bu3SnN3 to give, after hydrolysis with 6NHCl, cis-(1)-4-[2-[1(2)-H-tetrazol-5-yl)ethyl]-2-piperidinecarboxylic acid. I blocked N-methyl-D-aspartic acid-induced lethality in mice with min. ED of 10-160 mg/kg i.p.

23 ANSWER 11 OF 25

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- TI Axon-regenerating agents containing phosphatidylinositol, phosphatidylcholine, phosphatidylserine, and/or sphingomyelin
- AB Axon-regenerating agents contain natural or synthetic phosphatidylinositol, phosphatidylcholine, phosphatidylserine, and/or sphingomyelin. Dipalmitoylphosphatidylcholine at 100 .mu.g/mL exhibited remarkable axon regeneration. An injectable emulsion was formulated contg. phosphatidylcholine-contg. egg yolk phospholipid 6, soybean oil 50, and glycerin 12.5 g.

23 ANSWER 12 OF 25

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- TI Development and selective neurodegeneration in cell cultures from different hippocampal regions
- AB Previous studies have shown that pyramidal neurons in hippocampal regions CA1 and CA3 are selectively vulnerable in several neurodegenerative disorders and that a subpopulation of pyramidal neurons in cell cultures of embryonic hippocampus are sensitive to glutamate neurotoxicity. To det. whether the patterns of cell loss seen in situ correlate with intrinsic differences in neuronal sensitivities to glutamate-induced degeneration acquired during development, the authors characterized cultures established from different regions of postnatal rat hippocampus and then examd. neuronal sensitivity to glutamate. Tissue corresponding to the dentate gyrus (DG) and regions CA1, CA2, and CA3 of Ammon's horn was removed by microdissection from transverse hippocampal slices and was used to establish cultures of dissociated cells. Cultures from all 4 regions contained 3 major morphol. classes of neurons; pyramidal-like, bipolar, and stellate. Pyramidal-like neurons comprised the majority of neurons in all cultures; these neurons extended one long and branching axon, and one or more short dendrites. Immunocytochem. showed that all neurons possessed high levels of glutamate-like and GABA-like immunoreactivity when grown in isolation. In contrast, when bipolar and pyramidal neurons were cultured in contact with glial cells, glutamate and GABA immunoreactivity were selectively reduced in the bipolar and pyramidal cells, resp., suggesting that cell interactions influence neurotransmitter phenotype. Subpopulations of hippocampal neurons from each hippocampal region were vulnerable to glutamate-induced neurotoxicity. Bipolar and stellate cells were resistant to glutamate, whereas pyramidal-like neurons showed varying degrees of sensitivity to glutamate depending upon which region they were taken from. Expts. with specific glutamate receptor agonists and antagonists demonstrated that both non N-methyl-D-aspartic acid (NMDA) receptors and NMDA receptors mediated glutamate-induced degeneration. There were clear differences in the vulnerability of the pyramidal-like neuron populations in cultures from the different hippocampal regions. The rank order of the vulnerability of

between regions in culture was: DG<CA2<CA3<CA1. This pattern of selective vulnerability in cell culture corresponds directly to the pattern of selective cell loss seen in situ in Alzheimer's disease, epilepsy, and stroke suggesting that intrinsic neuronal differences in glutamate sensitivity may be involved in these disorders.

L23 ANSWER 13 OF 25

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- TI 2-(4-Allyl-1-piperazinyl)-4-pentyloxyquinazoline, processes for its production, and cerebral dysfunction remedy comprising it as active ingredient
- 4B Quinazoline deriv. I (R = (CH₂)₄Me, R₁ = Q) (II) useful as cerebral dysfunction remedy, was prepd. by, e.g., reaction of I (R = Cl, R₁ = Q) (III) with Me(CH₂)₄OH. POCl₃ (10 mL) was added to 10 g 2-(4-allyl-1-piperazinyl)-4(3H)-quinazolinone (IV) (prepn. given) and the mixt. was refluxed 3 h to give 10 g III. To a suspension of 3.0 g III in DMF, were added 1 l-pentanol and 0.5 g NaH under ice-cooling and then the mixt. was stirred 4 h at room temp. to give II. II·2HCl showed the activity of inhibiting formation of lipid peroxide (antioxidant activity) with an IC₅₀ of 152 μM which was ~~data~~ by the amt. of malonaldehyde formed in rats. Tablets (200 mg) were prepd. from II·2HCl 100, lactose 890, cryst. cellulose 900, CM-cellulose Ca 70, talc 25, and Mg stearate 15 g.

L23 ANSWER 14 OF 25

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- TI Preparation of pharmaceutically active heterocyclic amines and their use for treating head injury, spinal trauma, stroke, etc.
- 4B The arom. amines, alkylamines, bicyclic amines, cycloalkylamines, arom. bicyclic amines, hydroquinoneamines, amino ethers, and bicyclic amino ethers, which are individually represented by Markush formula, e.g. bicyclic amines I [W = O, S, NH, C1-3 alkylimino; n = 0, 1, or 2; R₇ = H, C1-4 alkyl, C1-4 alkyl, C1-4 alkylcarbonyl, PhCO, prodrug (e.g. PO₂O-, COCH₂CONHCH₂SO₂O-, or COCH:CHCO₂-); R₁₀-R₁₂ = H, Me; when R₂₅ = R₂₆ = H, R₁₆ = .alpha.-R₁₇:.beta.-R₁₈ where one of R₁₇ and R₁₈ = H, Me, Et, or Ph and the other is COM (M = substituted NH₂, heterocyclic amino; or C:CON:NCQ:CH where Q = 2-pyridinyl), (CH₂)_pCOM (p = 1-6), (CH₂)_qM (q = 1-6) or CO₂(CH₂)_rM (r = 2-6); when n = 0, R₁₆ = R₁₉:R₂₀ where one of R₁₉ and R₂₀ taken together with R₂₅ forms a second bond between the C atoms to which R₁₆ and R₂₅ are attached and the other = M-substituted groups described for R₁₆; when n = 1, R₂₅R₂₆ = bond between the C atoms to which R₂₅ and R₂₆ are attached; the original Markush definition was not completed.], useful as pharmaceuticals for treatment of head injury, spinal trauma, stroke and a no. of other related injuries and conditions (no data), are prepd. A mixt. of 6-bromohexanol, 2,6-bis(1-pyrrolidinyl)-4-(1-piperazinyl)-1,3,5-triazine, K₂CO₃, and NaI in MeCN was refluxed to give 4-[4,6-bis(1-pyrrolidinyl)-1,3,5-triazin-2-yl]-1-piperazinehexanol.

L23 ANSWER 15 OF 25

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- TI Preparation of 3-indolepyruvic acid derivatives and pharmaceutical use thereof
- 4B The title compds. II; X = C1-4 alkoxy, cyclohexyloxy, PhCH₂O, C1-4 (di)alkylamino, (di)cyclohexylamino, PhCH₂NH, (PhCH₂)₂N, amino acid residue], useful as central nervous system (CNS) agents, are prepd. Hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl were added to a soln. of I (X = OH) in THF under Ar and cooling, followed by Me₂NH·HCl and 4-methylmorpholine to give 35% amide I (X = Me₂N). In an audiogenic convulsion test, I (X = OH) and its Mg salt showed 33%

with tryptophan and 65% with controls. I also protected against N-methyl-D-aspartic acid-induced convulsion at 1 g/kg i.p. in mice, with a death rate of 3/9, vs. 8/10 of controls.

23 ANSWER 16 OF 25

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II Preparation of substituted imidazolylalkylpiperazines and -diazepines as pharmaceuticals

AB Title compds. I (R1,R4,R5 = aryl; R2 = aryl, alkyl, H; R3 = alkyl, OH, H; m = 2, 3; n = 0-2, or n = 0, 2 when R3 = OH; q = 0-3) useful as Ca entry blockers (no data) are prepd. To a refluxing soln. of N-(diphenylmethyl)piperazine and NaOH in EtOH-H2O (3:2) was added a soln. of 2-(4-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole.HCl (prepn. given) in EtOH-H2O (3:2) to give 70% I (R1 = p-MeC6H4; R2 = Me; R3 = H; R4 = R5 = Ph; m = 2; n = q = 0) (II). II.3HCl at 5 mg/kg p.o. showed approx. 5.7, approx. 9.5, and approx. 11.8 mL urine collected after 1, 3, and 6 h, resp. of administration in normotensive rats, vs. approx. 3.3, approx. 7.3, and approx. 5.6 mL for control, resp. and no significant kaliuretic effects were obsd. A tablet was formulated contg. I 25, cornstarch 20, lactose 153, and Mg stearate 2 mg.

23 ANSWER 17 OF 25

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II Method and compositions containing enantiomer of analgesic opioid; agonist or antagonist for reducing neurotoxic injury

AB The adverse effects of neurotoxic malfunction are reduced by administration of an effective amt. of a mirror-image enantiomer of an analgesic opioid agonist or antagonist, esp. an opiate agonist having ring system I. Mixed cortical cell cultures, contg. both neuronal and glial elements were prepd. Exposure to 0.5 mM glutamate for 5 min resulted by the following day in disintegration of the majority of the neurons; many remaining neurons failed to exclude trypan blue dye. However, when dextrorphan (100 μ M) was added to the glutamate exposure soln., both the morphol. and the chem. evidence of glutamate neurotoxicity was markedly attenuated. Neurons protected by addn. of dextrorphan excluded trypan blue dye and remained morpholog. stable for at least several days.

23 ANSWER 18 OF 25

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II Treatment of cerebral disorder and skin disease by 1,3-dibutyl-7-(2-oxypropyl)xanthine

AB The title compd. (I) is useful in the treatment of cerebral disorders (e.g., dementia, Alzheimer's disease, etc.) and skin disease. I administered to rats restored the exptl. induced memory damage, indicating that I is effective in treating dementia and other disorders.

23 ANSWER 19 OF 25

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II Preparation of 5-aryl-3H-1,2,4-triazol-3-ones and their use in the treatment of neurodegenerative disorders

AB The title compds. (I; R = Cl-6 alkyl, alkoxy, OH, halo, CF3; R1 = H, Cl-6 alkyl; R2 = Cl-6 alkyl; X = Ph, naphthyl, heteroaryl; RnX = methylenedioxyphenyl; n, m = 0-2), useful for treatment of brain disorders (no data), were prepd. 1-(2-Thienyl)-4-methylsemicarbazide (prepn. given) was refluxed 23 h in 1 N aq. NaOH to give 5-(2-thienyl)-2,4-dihydro-4-methyl-3H-1,2,4-triazol-3-one.

- TI Xanthine derivatives, their preparation and pharmaceutical compositions containing them
- AB Xanthine derivs. I [R1, R2 = Bu, (CH₂)₂CH(OH)Me, (CH₂)₂CH(OH)CH₂OH, (CH₂)₂COMe, (CH₂)₂C(OR₄)(OR₅)Me; R₄, R₅ = C1-4 alkyl; R₄R₅ = C2-4 polymethylene (R1, R2 not both Bu); R₃ = CH₂CH(OH)Me, CH₂COMe, CH₂C(OR₆)(OR₇)Me; R₆, R₇ = C1-4 alkyl; R₆R₇ = C2-4 polymethylene] and their salts, were prepd. I have a protective effect against the consequences of cerebral metabolic inhibition and also improve data acquisition or retrieval following transient forebrain ischemia. I are also active in increasing the O₂ tension in ischemic skeletal muscle. I also act as phosphodiesterase inhibitors and elevate cAMP levels. 3-Butylxanthine was alkylated with ClCH₂COMe and NaOEt in EtOH to give 30.6% 3-butyl-1-(2-oxopropyl)xanthine which was acetalized with (HOCH₂)₂ to give 2-methyl-2-[(3-butylxanthin-7-yl)methyl]-1,3-dioxolane. Reacting with ClCH₂CH₂COMe and K₂CO₃ in DMF gave 2-methyl-2-[[1-(3-oxobutyl)-3-butylxanthin-7-yl]methyl]-1,3-dioxolane which was deacetalized to give 1-(3-oxobutyl)-3-butyl-7-(2-oxopropyl)xanthine. NaBH₄ redn. gave 1-(3-hydroxybutyl)-3-butyl-7-(2-hydroxypropyl)xanthine (II). At 2 times, 30 mg/kg in rats, II gave 40% redn. in Et₃Sn-induced cerebral edema formation.

L23 ANSWER 21 OF 25

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- TI Preparation of pyrido[1,2-a]indoles for treatment of cerebrovascular disorders
- AB The title compds. II; R1 = H, C1-6 alkyl, C1-6 alkoxy, halo; R2, R3 = H, R₂R₃ = bond; R4, R5 = H; R₄R₅ = O; R₆ = (un)substituted Ph, substituted phenylalkyl, substituted phenylalkenyl; R7 = H; C1-4 alkyl and their salts were prepd. 10-[2-14-(Methoxycarbonylmethylamino)benzoyl]aminoethyl]-6,7,8,9-tetrahydropyrido[1,2-a]indole-HCl (obtained in 5 steps from 6,7,8,9-tetrahydropyrido[1,2-a]indole-10-propionic acid), in THF, was added to LiAlH₄ and refluxed to give I [R1, R4, R5, R7 = H; R₂R₃ = bond; R₆ = 4-(HOCH₂CH₂NH)C₆H₄CH₂.cntdot.2HCl] (II). Rats intoxicated with 2 mg Et₃SiCl/kg once a day for 5 days and also given II orally twice daily as aq. soln. or suspension at a dose 1 mL/100 g body-wt. showed a protection index of 47%.

L23 ANSWER 22 OF 25

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- TI Determination of regional glucose metabolism in brain by FDG and PET with reference to drug effects and changes in the course of cerebrovascular disease and dementia
- AB The detn. of cerebral regional glucose metab. in brain by positron emission tomog. (PET) with [¹⁸F]fluoro-2-deoxy-D-glucose (FDG) was studied in healthy volunteers and in patients with acute cerebrovascular disease, intracerebral hemorrhage, dementia, and ischemic stroke. A mean glucose consumption rate of 29-32 .mu.mol/100g/min was obsd. in healthy volunteers, with the highest values being found in the visual cortex (45-50 .mu.mol/100g/min) and striatum (42-46 .mu.mol/100g/min) and lowest in the white substance (15-22 .mu.mol/100g/min). Changes in glucose metab. in the course of disease are traced, and changes during therapeutic intervention described.

L23 ANSWER 23 OF 25

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- TI Dysfunction of central cholinergic system in hyperkinetic rats,

4B. Single exposure of rats to postnatal anoxia caused a long lasting dysfunction of the cholinergic system as expressed by a gradual decline in choline acetyltransferase (ChAT) activity throughout development and maturity. Decreased levels or released acetylcholine during development and maturity could cause a compensatory increase in postsynaptic receptors, hyperkinesia, and learning deficits, all these being changes found in the anoxia rats during their development. The decline in ChAT activity which is presently found in the hippocampus and caudate is probably not restricted to these 2 areas; that other cholinergic areas in the brain are also affected by anoxia is assumed. The first compensatory response to decreased levels of acetylcholine is the increase in d. of postsynaptic muscarinic receptors, which mature relatively earlier than the presynaptic enzymes. With further development, however, a compensatory increase in choline uptake was found with return to normal behavior and a decrease in postsynaptic receptor d. to normal values. A lack of a compensatory increase in choline uptake in some brain areas other than the hippocampus, or its decline with age, may cause severe dysfunction of the cholinergic system, esp. in old age. Anoxia-treated rats may therefore serve as a model for Alzheimer disease in which there is a dysfunction of the central cholinergic system.

23 ANSWER 24 OF 25

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- 11 Phosphorus-31 nuclear magnetic resonance studies of anoxia and ischemia in animal brain and of human brain in Alzheimer's and Huntington's diseases
- 4B A review with 10 refs. of the changes occurring in the brain concns. of various phosphates in the title diseases.

23 ANSWER 25 OF 25

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- 11 Biological plasticity of the aging brain
- 4B Normal cerebral aging is assocd. with significant redns. of the concns. of glucose, fructose 1,6-diphosphate, pyruvate, malate, ATP, and creatine phosphate in brain cortex of male Wistar rats. The effect of a 15-min severe arterial hypoxemia on glucose and energy metab. of the aging brain yield similar results in 2-yr-old rats and 1-yr-old controls. Severe arterial hypoxemia, however, seems to cause less pronounced reactions in glycolytic flux and citric acid cycle intermediates. A 15-min complete cerebral ischemia produced changes which were in general similar in 1- and 2-yr-old rats. Evidently the aging brain suffers from the capacity to meet the demands under stress situations such as severe arterial hypoxemia and ischemia, i.e. the plasticity of the aging brain is reduced. A 3-wk i.p. application of vincristine induced changes in the glycolytic breakdown of glucose in brain cortex comparable to those which are found in dementia of Alzheimer type. This animal model may be a useful tool for dementia research.

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